

Original article

Single-agent gemcitabine *versus* cisplatin–etoposide: Early results of a randomised phase II study in locally advanced or metastatic non-small-cell lung cancer

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Summary

Background: This randomised study was designed to determine the response rate, survival and toxicity of single-agent gemcitabine and cisplatin–etoposide in chemo-naïve patients with locally advanced or metastatic non-small-cell lung cancer.

Patients and methods: Gemcitabine 1,000 mg/m² was given as a 30 min intravenous infusion on days 1, 8, 15 of a 28-day cycle, cisplatin 100 mg/m² on day 1, and etoposide 100 mg/m² on days 1 (following cisplatin), 2 and 3. Major eligibility criteria included histologically confirmed non-small-cell lung cancer, measurable disease, Zubrod PS 0–2; no prior chemotherapy, no prior radiation of the measured lesion, and no CNS metastases.

Results: 146 patients were enrolled, 71 patients on gemcitabine and 75 patients on cisplatin–etoposide. Patient characteristics were well matched across both arms. Sixty-six gemcitabine patients and 72 cisplatin–etoposide patients were evaluable. Partial responses were seen in 12 gemcitabine patients

(18.2%; 95% CI: 9.8–30) and 11 cisplatin–etoposide patients (15.3%; 95% CI: 7.9–25.7). Early indications show no statistical differences between the two treatments with respect to time to disease progression or survival. Haematological and laboratory toxicity were moderate and manageable. However, hospitalisation because of neutropenic fever was required for 6 (8%) cisplatin–etoposide patients but not for any gemcitabine patients. Non-haematological toxicity was more pronounced with significant differences in nausea and vomiting (grade 3 and 4: 11% gemcitabine vs. 29% cisplatin–etoposide; despite the allowance for 5-HT₃ antiemetics during the first cycle of cisplatin–etoposide), and alopecia (grade 3 and 4: 3% gemcitabine vs. 62% cisplatin–etoposide).

Conclusions: In this randomised study, single-agent gemcitabine was at least as active but better tolerated than the combination cisplatin–etoposide.

Key words: cisplatin, etoposide, gemcitabine, non-small-cell lung cancer, randomised phase II study

Introduction

The systemic treatment currently recommended in patients with advanced non-small-cell lung cancer (NSCLC) is cisplatin-based combination chemotherapy [1]. However, because of the toxicity of cisplatin, combination treatment can only be administered to patients in good general health, which is the case only for a minority of stage IV patients. Gemcitabine is a new nucleoside analogue with major antitumour efficacy in various solid tumours in contrast to cytosine-arabinoside which is not active in solid tumours. Over the last few years a number of phase II studies have been undertaken with gemcitabine as a single agent [2–5] and in combination [6, 7] in patients with NSCLC. The schedule currently recommended for gemcitabine is a 1,000 mg/m² 30-minute intravenous infusion given on days 1, 8 and 15 of a 28-day cycle. Phase II studies with gemcitabine in the

first-line treatment of advanced NSCLC have produced consistent response rates of 20% with a median survival of 38 weeks [2–5]. In addition to its objective antitumour activity, gemcitabine is one of the first drugs with documented data on symptom benefit. Several phase II studies have also shown that gemcitabine is well tolerated, is easy to administer on an outpatient basis, and is effective in non-small-cell lung cancer, with activity in a range that can be expected for cisplatin-containing combination regimens. Gemcitabine can be particularly beneficial for the therapy of elderly and unfit patients as well as for the palliation of tumour-related symptoms [8]. It therefore seemed logical to compare gemcitabine as a single agent with a standard combination chemotherapy (such as cisplatin–etoposide) to establish whether better tolerated treatment could be given to patients who could not receive cisplatin-containing chemotherapy because of its toxicity.

Patients and methods

Major eligibility criteria

Patients were included in the study only if they met the following criteria: histological diagnosis of NSCLC, stage IIIa (if inoperable), IIIb, or IV, according to the American Joint Committee of Cancer (AJCC); no prior chemotherapy; no prior radiation therapy except where the irradiated area was not the only source of measurable disease; performance status of ≤ 2 on the Zubrod scale; adequate bone marrow reserve (white blood cell count $\geq 3.5 \times 10^9/l$, platelets $\geq 100 \times 10^9/l$, haemoglobin ≥ 100 g/l, age ≥ 18 years. Patients were excluded from the study if they had central nervous system metastases, bilirubin > 1.5 times normal, prothombin time or activated partial thromboplastin time > 1.5 times control, ALT or AST > 3 times normal (or up to 5 times normal in patients with known liver metastases), serum calcium levels above the normal limits, pregnancy, breast feeding, serious concomitant systemic disorders, or concomitant treatment with nephrotoxic antibiotics.

Treatment

Patients were randomised to receive either gemcitabine or cisplatin-etoposide. Gemcitabine $1,000$ mg/m² was given as a 30-minute intravenous infusion on days 1, 8 and 15 of a 28-day cycle. Cisplatin 100 mg/m² was given intravenously on day 1 of the 28-day cycle, and etoposide 100 mg/m² was administered intravenously on day 1 (following cisplatin), 2 and 3 of each 28-day cycle. Patients could remain in the study for up to six cycles or until disease progression was noted.

Study design

This was an open label randomised trial carried out with ethical committee approval. Patients were stratified according to stage, performance status and investigator centre using the algorithm outlined by Pocock and Simon [9].

Concomitant therapy

Patients were allowed to take medication for other illnesses provided this was documented. Colony stimulating factors were also allowed for prolonged myelosuppression, i.e., lasting five days or more (in fact no patient experienced such prolonged myelosuppression and no patients received growth factors). Prednisone 10 mg/m² was permitted for other diseases. In the cisplatin-etoposide arm, prophylactic 5-HT₃ receptor blocking agents and steroids (dexamethasone 20 mg or equivalent) were permissible. In the gemcitabine arm, prophylactic 5-HT₃ antiemetics were not permitted at dose 1 cycle 1 but were allowed at subsequent doses depending on the severity of nausea and vomiting following the first dose. Patients with disease progression requiring other forms of specific antitumour therapy were removed from this study. If an existing lesion became more painful and was not accompanied by other objective changes indicating disease progression, palliative local radiotherapy was permitted without discontinuing the patient, provided other measurable sites were being assessed.

Discontinuations

Patients were discontinued from the study under the following circumstances: if there was evidence of progressive disease; if the attending physician thought the change of therapy was in the best interest of the patient; if the patient requested a discontinuation; if the patient experienced unacceptable drug toxicity; if the patient's best response was achieved; if chemotherapy could not be administered to the patient within four weeks from the time of the last treatment. Time to treatment failure was measured from the time of first dose of the study drug(s) to discontinuation. Patients were kept on study for up to six cycles.

Qualification for analysis

All patients who received at least one dose of gemcitabine or cisplatin-etoposide were evaluated for safety. All patients randomised to treatment and meeting the eligibility criteria were considered qualified for objective tumour response assessment (using standard WHO response criteria) and for analysis of the time to event parameters. In addition, an intent-to-treat analysis of all randomised patients was made.

Dose adjustments (see Table 1) within a cycle were based on weekly absolute granulocyte and platelet counts, taken on the day of therapy. Serum creatinine was obtained prior to each cycle in order to determine calculated creatinine clearance and ongoing clinical assessment of non-haematological toxicities.

Results

Between June and December 1995, 146 patients were enrolled, 71 patients in the gemcitabine arm, and 75 patients in the cisplatin-etoposide arm. For this early analysis, information was collected as of July first 1996 (all patients off trial). The data are therefore fully mature with respect to response rate but not for time to event (i.e., disease progression and survival). Patient demographics and baseline disease characteristics were well matched across treatment arms (Table 2) with slightly more cases of Zubrod performance status grade 2 in the gemcitabine arm, and slightly more stage IIIa disease in a cisplatin-etoposide arm. The median age in both treatment groups was 59 years. In the gemcitabine and cisplatin-etoposide groups there were, respectively, 29 and 28 female patients, 37 and 31 patients with adenocarcinoma, and 22 and 24 patients with squamous cell carcinoma.

Treatment

The number of cycles completed by patients ranged from one to six on both treatment arms. The median

Table 1. Dose reductions and omissions made in the event of toxicity.

Toxicity	% full dose gemcitabine	% full dose etoposide	% full dose cisplatin
Granulocytes ($\times 10^9/l$)			
1000–1500	75	50	50
500–999	50	Omit	Omit
< 500	Omit	Omit	Omit
Platelets ($\times 10^9/l$)			
75.0–99.9			
50.0–74.9			
< 50.0			
Creatinine clearance (ml/min)			
40–60	100	100	75
< 40	100	100	Omit
Non-haematological (first cycle)			
WHO grade 3 ^a	50 or omit	100	100
WHO grade 4	Omit	100	100
Non-haematological (subsequent cycles)			
WHO grade 3 ^a	75	100	100
WHO grade 4	50 or omit	100	100

^a Except nausea/vomiting or alopecia.

Table 2. Characteristics of enrolled patients.

Patients	GEM	C/E
(n)	71	75
Age (yrs)		
Median	59	59
Range	32–80	33–78
Sex		
Female	29	28
Male	42	47
Zubrod PS		
0	16	17
1	43	51
2	12	7
Stage		
IIIA	4	6
IIIB	13	13
IV	54	56
Histology		
Adenocarcinoma	37	31
Squamous	22	24
Other	12	20

(and mean) number of cycles received per patient was 2.0 (3.0) for gemcitabine and 3.0 (3.0) for cisplatin–etoposide. Overall, 99% of the protocol-defined injections were administered in both arms with 93% and 95% respectively given at the assigned doses. Dose reductions were not common, 6% with gemcitabine and 4% with cisplatin–etoposide. The mean dose intensities were: gemcitabine 967 mg/m² (days 1, 8 and 15 of a 28 day cycle), cisplatin 97 mg/m² (day 1), and etoposide 99 mg/m² (days 1, 2 and 3).

Efficacy

Sixty-six (93%) gemcitabine patients and 72 (96%) cisplatin–etoposide patients were evaluable for efficacy. Five gemcitabine patients (7%) were not evaluable for efficacy (2 patients with rapid disease progression, three patients with no bidimensionally measurable lesions). Three cisplatin–etoposide patients (4%) were not evaluable for efficacy (2 patients with rapid disease progression, one patient with no bidimensionally measurable lesions). Efficacy data are shown in Table 3. With gemcitabine, 12 patients had a partial response for an overall response rate of 18.2% (95% CI: 9.8%–30%). With cisplatin–etoposide, 11 patients had a partial response for an overall response rate of 15.3% (95% CI: 7.9%–25.7%). At the time of data cut-off, there were no statistical differences between the two treatment arms with respect to time and progression and survival (Table 3).

Toxicity profile

Haematological toxicity was not a clinical problem in either treatment arm (Table 4). Normal platelet levels were reported for 87% of gemcitabine patients and 94% of cisplatin–etoposide patients. Two patients experienced grade 3 toxicity with gemcitabine but no patient showed grade 4 toxicity. There was no need for platelet trans-

Table 3. Efficacy.

	GEM n (%)	C/E n (%)
Partial response	12 (18.2)	11 (15.3)
95% CI	(9.8–30)	(7.9–25.7)
Stable disease	30 (45.5)	35 (48.6)
Time to progression		
Median ^a	4.2 mo	4.9 mo
95% CI	(2.9–5.6)	(3.2–5.8)
	<i>P</i> > 0.90	
Survival		
Median ^b	6.6 mo	7.6 mo
95% CI	(4.9–7.1)	(5.6–9.6)
	<i>P</i> > 0.90	

^a Patients progression free: 35% for GEM; 38% for C/E.

^b Patients still alive: 50% for GEM; 46% for C/E.

Table 4. Toxicity profile.

Maximum WHO grades (%)		0	3	4
Haematological				
Neutrophils	GEM	70	6	2
	C/E	73	3	12
Haemoglobin	GEM	43	4	0
	C/E	34	3	0
Platelets	GEM	87	2	0
	C/E	94	0	0
Liver				
Alk Phos	GEM	72	1.6	0
	C/E	87	0	1.6
ALT	GEM	70	0	0
	C/E	91	0	0
AST	GEM	77	0	0
	C/E	95	0	0
Renal				
Bilirubin	GEM	98	0	0
	C/E	100	0	0
BUN	GEM	93	0	0
	C/E	95	0	0
Symptomatic				
Hair	GEM	97	3	0
	C/E	0	60	2
Nausea/vomiting	GEM	45	11	0
	C/E	11	25	4
Neurohearing	GEM	98	0	0
	C/E	84	6	0
Dyspnoea	GEM	76	4	6
	C/E	81	4	0

fusions. Anaemia was usually mild. Grade 3 haemoglobin toxicity was seen in 4% of gemcitabine patients and 3% of cisplatin–etoposide patients, but no grade 4 toxicity was seen in either group. However, red cell transfusions were given to nine gemcitabine patients and to 17 cisplatin–etoposide patients. A normal neutrophil count was reported in 70% of gemcitabine patients, and in 73% of cisplatin–etoposide patients. Grade 3 and 4 toxicity was seen in 6% and 2% of gemcitabine patients and in 3% and 12% of cisplatin–etoposide patients. Hospitalisation because of neutropenic fever was required for 6 (8%) cisplatin–etoposide patients but was not necessary for any gemcitabine patients.

Laboratory toxicity was clinically insignificant (Table 4). The incidence of alopecia was minimal with gemcitabine (97% of patients had no hair loss (Table 4), whereas 60% and 2% of cisplatin–etoposide patients had grade 3 and 4 hair loss. The majority of cisplatin–etoposide patients reported nausea and vomiting with about 30% grade 3 and 4 toxicity; only 11% of cisplatin–etoposide patients experienced no nausea and vomiting. With gemcitabine, grade 3 nausea and vomiting was only 11% with no grade 4 toxicity; as many as 45% of the patients had no nausea and vomiting. Neuro-hearing toxicity was greater with cisplatin–etoposide than with gemcitabine.

Grade 3 pulmonary toxicity (dyspnoea at rest) was seen in three patients in each treatment arm. Grade 4 pulmonary toxicity (dyspnoea requiring bed rest) was experienced in four patients on gemcitabine. Drug causality could not be excluded for two patients in each treatment arm. For five of the seven patients in the gemcitabine arm dyspnoea was attributed to the primary lung cancer.

Discussion

The results achieved by chemotherapy in advanced, non-small-cell lung cancer continue to be unsatisfactory and are largely palliative in nature. Cisplatin-based combination therapy is currently the standard recommended treatment [10]. This recommendation is based upon the higher response rates and the slightly improved survival benefit, small in extent but statistically significant, which can be attributed to this combination therapy when compared with single-agent therapy. For example, the combination cisplatin–etoposide produces response rates of 11%–30% [11, 12] and a median survival of 16–42 weeks, with a pooled median survival of 27 weeks [10, 13–18]. In 1989 an ECOG study showed that single-agent carboplatin produced a response rate of 9% and a median survival of 30 weeks [19]. Although countless studies have demonstrated that the inclusion of platinum agents in combination chemotherapy produces better results than early combinations without cisplatin, the use of chemotherapy for the cytostatic therapy of advanced NSCLC has not increased appreciably over the last 15 years and remains comparatively low [20]. In the UK, only about 20% of the patients with stage IV NSCLC are treated with chemotherapy. The reason for the low acceptance of chemotherapy may be that the current standard combinations are considered to be too toxic to be used beneficially in older and polymorbid patients. The perception in the majority of clinicians is that the quality of a shorter life without combination chemotherapy is more worthwhile than a longer life but one in which patients suffer greater side effects.

In this respect the concept of single-agent therapy appears to be an attractive alternative when the ultimate goal of palliation can be similarly achieved by a less toxic chemotherapy with increased practicability, i.e., the possibility of outpatient administration. Random-

ised studies have shown that combination therapy is usually statistically superior to single-agent therapy, not only in response rates but also in life expectancy [19, 21–29]. However, in the earlier studies no systematic attempt was made to assess the effect of chemotherapy on the patient's quality of life.

We initiated a randomised study to compare gemcitabine with cisplatin–etoposide in order to determine whether single-agent gemcitabine would prove as effective as established combination chemotherapy. At the same time we were interested to see whether gemcitabine would be better tolerated, so that it could be used in patients in which cisplatin-based chemotherapy would be too toxic.

The single-agent response rate for gemcitabine (18.2%) in this randomised study is comparable to that seen with the other newer agents (vinorelbine, the taxanes and camptothecans), and is promising given the acceptable toxicity profile of gemcitabine. In this randomised setting we have shown that single-agent gemcitabine is indeed as effective as the traditionally recommended combination of cisplatin–etoposide. Because of the short duration of the ensuing follow-up, it is not yet possible to provide accurate time to progression or median survival data. However, to date no great differences have been seen, with the median survival currently at 6.6 months for gemcitabine *versus* 7.6 months for cisplatin–etoposide ($P > 0.90$).

Non-haematological toxicity was significantly better in gemcitabine patients than in cisplatin–etoposide patients. The incidence and intensity of nausea and vomiting was negligible with gemcitabine, with nothing reported over grade 3. By contrast, more than half of the cisplatin–etoposide patients reported grade 3 and 4 toxicity, despite the fact that 5-HT₃ receptor blocking agents and steroids were given prophylactically with the first cisplatin–etoposide dose. In the gemcitabine arm no such prophylactic drugs were permitted for the first dose, although they were allowed for subsequent doses if the patients experienced nausea or vomiting following the first administration. Similarly, alopecia was minimal with gemcitabine whereas the majority of cisplatin–etoposide patients experienced grade 3/4 alopecia. Some studies have shown that patients treated with gemcitabine can develop pulmonary difficulties [30]. In our study the majority of patients did not experience pulmonary toxicity.

Haematological toxicity was more pronounced with cisplatin–etoposide compared with gemcitabine. Anaemia was usually mild in both treatment arms, although red cell transfusions had to be administered to twice as many cisplatin–etoposide patients (compared with gemcitabine). Furthermore, there was no neutropenic fever or sepsis with gemcitabine whereas 8% of patients on cisplatin–etoposide had to be hospitalised for neutropenic sepsis. Thrombocytopenia was generally mild in both treatment arms, although in the cisplatin–etoposide arm, one haemorrhage did occur and several platelet transfusions were required.

In conclusion, we believe that this randomised study provides strong supporting evidence for the efficacy of gemcitabine in NSCLC. Single-agent gemcitabine appears to be as active but at the same time much less toxic than the combination cisplatin-etoposide in the first-line chemotherapy of advanced NSCLC. With less toxic anticancer drugs like gemcitabine, the physician now has greater choice in choosing treatment. In patients where quality of life is particularly important and patients are unable to tolerate the toxicities of traditional cisplatin-based chemotherapy, gemcitabine offers lower toxicity yet activity which is equivalent to that of other single agents. On the other hand, where physicians want to aim for higher response rates and treat more intensively they can use a combination chemotherapy using cisplatin or one or more of the newer agents (e.g., vinorelbine, gemcitabine, taxanes, camptothecans).

References

- Non-small-Cell Lung Cancer Collaborative Group. Chemotherapy in non-small-cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995; 311: 899-909.
- Abratt RP, Bezwoda WR, Falkson G et al. Efficacy and safety profile of gemcitabine in non-small-cell lung cancer: A phase II study. *J Clin Oncol* 1994; 12: 1535-40.
- Anderson H, Lund B, Bach F et al. Single-agent activity of weekly gemcitabine in advanced non-small-cell lung cancer: A phase II study. *J Clin Oncol* 1994; 12: 1821-6.
- Gatzemeier U, Shepherd FA, Le Chevalier T et al. Activity of gemcitabine in patients with non-small-cell lung cancer: A multicenter extended phase II study. *Eur J Cancer* 1996; 32(2): 243-8.
- Fossella FV, Lippman SM, Shin DM et al. Maximum-tolerated dose defined for single-agent gemcitabine: A phase I dose-escalation study in chemotherapy-naïve patients with advanced non-small-cell lung cancer. *J Clin Oncol* 1997; 15: 310-6.
- Crino L, Scagliotti G, Marangolo M et al. Cisplatin-gemcitabine combination in advanced non-small-cell lung cancer: A phase II study. *J Clin Oncol* 1997; 15: 297-303.
- Abratt RP, Bezwoda WR, Goedhals L et al. Weekly gemcitabine with monthly cisplatin: Effective chemotherapy for advanced non-small-cell lung cancer. *J Clin Oncol* 1997; 15: 744-9.
- Ardizzoni A, Martin C. Gemcitabine toxicity profile and efficacy unaffected by age in advanced non-small-cell lung cancer (NSCLC). *Ann Oncol* 1994; 5 (Suppl 8): 60 (Abstr P295).
- Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; 31: 103-15.
- Crino L, Tonato M, Darwish S et al. A randomised trial of 3 cisplatin containing regimens in NSCLC. A study of the Umbrian Lung Cancer Group. *Cancer Chemotherapy Pharmacol* 1990; 26: 52-6.
- Ruckdeschel JC. The role of standard dose etoposide in the management of NSCLC. *Semin Oncol* 1992; 10: 39-44.
- Bonomi P, Finkelstein D, Chang A. Phase II trial of acivicin *versus* etoposide-cisplatin in non-small-cell lung cancer. An Eastern Cooperative Oncology Group study. *Am J Clin Oncol* 1994; 17: 215-7.
- Dhingra HM, Valdivieso M, Carr DT et al. Randomised trial of three combinations of cisplatin with vindesine and/or VP-16 in the treatment of advanced NSCLC. *J Clin Oncol* 1985; 3: 176-83.
- Hainsworth JD, Johnson DH. Chemotherapy of advanced NSCLC: A randomised trial of three cisplatin-based chemotherapy regimens. *Am J Clin Oncol* 1989; 12: 345-9.
- Klastersky J, Sculier JP, Lacroix H et al. A randomised study comparing cisplatin or carboplatin with etoposide in patients with advanced NSCLC. EORTC protocol 07861. *J Clin Oncol* 1990; 8: 1556-62.
- Ruckdeschel JC, Finkelstein DH, Ettinger DS et al. A randomised trial of the four most active regimens for metastatic NSCLC. *J Clin Oncol* 1986; 4: 14-21.
- Weick JK, Crowley J, Natale RB et al. A randomised trial of five cisplatin containing regimens in patients with metastatic NSCLC. A Southwest Oncology Group Study. *J Clin Oncol* 1991; 9: 1157-62.
- Klastersky J, Sculier JP, Ravez P et al. A randomised study comparing a high and a standard dose of cisplatin in combination with etoposide in the treatment of advanced NSCLC. *J Clin Oncol* 1986; 4: 1780-6.
- Bonomi PD, Finkelstein DM, Ruckdeschel JC et al. Combination chemotherapy *versus* single agents followed by combination chemotherapy in stage IV non-small-cell lung cancer: A study of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1989; 7: 1602-13.
- Slevin ML, Stubbs L, Plant HJ et al. Attitude to chemotherapy: Comparing views of patients with cancer with those of doctors, nurses and general public. *BMJ* 1990; 300: 1458-60.
- Einhorn LH, Loehrer PJ, Williams SD et al. Random prospective study of vindesine *versus* vindesine plus cisplatin, plus mitomycin in advanced non-small-cell lung cancer. *J Clin Oncol* 1986; 4: 1037-43.
- Sorensen B, Hansen HH, Dambernowsky P et al. Chemotherapy for adenocarcinoma of the lung (WHO III): A randomised study of vindesine *versus* lomustine, cyclophosphamide, and methotrexate *versus* all four drugs. *J Clin Oncol* 1987; 5: 1169-77.
- Klastersky J, Sculier JP, Bureau G et al. Cisplatin *versus* cisplatin plus etoposide in the treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 1989; 7: 1087-92.
- Rosso R, Salvati F, Ardizzoni A et al. Etoposide *versus* etoposide plus high-dose cisplatin in the management of advanced non-small-cell lung cancer. *Cancer* 1990; 66: 130-4.
- Kawahara M, Furuse K, Nagoheha K et al. A randomized study of cisplatin *versus* cisplatin plus vindesine for non-small-cell lung cancer. *Cancer* 1991; 68: 714-9.
- Veeder MH, Jett JR, Su JO et al. A phase III trial of mitomycin C alone *versus* mitomycin C, vinblastine and cisplatin for metastatic squamous cell lung cancer. *Cancer* 1992; 70: 2281-6.
- Depierre A, Le Beau B, Chasting C et al. Results of a phase III randomized study of vinorelbine-cisplatin in non-small-cell lung cancer. *Proc Am Soc Clin Oncol* 1993; 12: 340.
- Giaccone G, Splinter T, Fester J et al. Cisplatin combined with teniposide improves response and survival over VM alone in non-small-cell lung cancer: A randomized trial of the EORTC Lung Cancer Cooperative Group. *Proc Am Soc Clin Oncol* 1993; 12: 331.
- Le Chevalier T, Brisgand D, Douillard JY et al. Randomized study of vinorelbine and cisplatin *versus* vindesine and cisplatin *versus* vinorelbine alone in advanced non-small-cell lung cancer: Results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994; 12: 360-7.
- Van Meerbeek J, Debruyne C, Postmus PE et al. Sequential phase II studies with paclitaxel and gemcitabine in malignant pleural mesothelioma. *Eur Resp J* 1996; 9 (Suppl 23): 400s.

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